Better Rejection-Free Survival at Three Years in Kidney Transplant Recipients With Model-Informed Precision Dosing of Mycophenolate Mofetil

Claire Villeneuve[1,2,3,†], Antoine Humeau[2,3,†], Caroline Monchaud[1,2,3], Marc Labriffe[1,2,3], Jean-phillipe Rerolle[2,3,4,5], Lionel Couzi[6], Pierre-François Westeel[7], Isabelle Etienne[8], Nassim Kamar[9,10,11], Mathias Büchler[3,12,13], Antoine Thierry[3,14] and Pierre Marquet[1,2,3,*]

The clinical impact of individual dose adjustment of mycophenolate mofetil is still debated, due to conflicting results from randomized clinical trials. This retrospective study aimed to compare 3-year rejection-free survival and adverse effects between adult kidney transplant recipients (KTRs) with or without mycophenolate mofetil model-informed precision dosing (MIPD). MIPD is defined here as mycophenolic acid area under the curve (AUC_{0-12h}) estimation using a limited sampling strategy, pharmacokinetic models and Bayesian estimators; dose recommendation to reach AUC_{0-12h} = 45 mg.h/L; using a widely used online expert system. The study, nested in two multicenter prospective cohort studies, focused on patients who received a mycophenolate drug and were followed up for 1–3 years. Mycophenolate mofetil MIPD was prescribed as per local practice, on a regular basis, when deemed necessary, or not at all. The MIPD group included 341 KTRs and the control group 392. At 3 years, rejection-free survival was respectively 91.2% and 80.6% ($P < 0.001$) and the cumulative incidence of rejection 5.08% vs. 12.7% per patient × year (hazard ratio = 0.49 (0.34, 0.71), $P < 0.001$), corresponding to a 2.5-fold reduction. Significant association with rejection-free survival was confirmed in patients at low or high risk of rejection ($P = 0.017$ and 0.013) and in patients on tacrolimus, but not on cyclosporine ($P < 0.001$ and 0.205). The mycophenolate mofetil MIPD group had significantly more adverse effects, but most occurred before the first AUC_{0-12h}, suggesting some may be the reason why MIPD was ordered.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

☑ The summaries of product characteristics of mycophenolic acid drugs, given to most kidney transplant recipients (KTRs), recommend standard doses, despite huge between-patient pharmacokinetic variability. Sixteen years ago, a randomized controlled trial demonstrated that mycophenolate mofetil dose adjustment based on the area under the concentration-time curve over 12 hours (AUC_{0-12h}) (called here mycophenolate mofetil model-informed precision dosing, or MIPD) significantly decreased the incidence of biopsy-proven acute graft rejection over the first year post transplantation in KTRs on cyclosporine. No evidence of a clinical benefit of this procedure beyond 1 year, or in patients on tacrolimus, has been published since.

WHAT QUESTION DID THIS STUDY ADDRESS?

☑ We investigated survival without rejection at 3 years post transplantation in KTRs on cyclosporine or tacrolimus, included in a prospective cohort, who happened to be exposed to mycophenolate mofetil MIPD or not (it was not part of the cohort protocol).

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

☑ We found that mycophenolate mofetil MIPD was associated with a 2.5-fold lower cumulative incidence of graft rejection and significantly better rejection-free survival at 3 years, overall as well as in patients at low or high risk of rejection, and particularly in patients on tacrolimus.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

☑ This new piece of (real-world) evidence may encourage more physicians performing kidney transplants to adopt mycophenolate mofetil model-informed precision dosing. It also paves the way for studies with longer patient follow-up and hard outcomes (death or graft loss), as well as for other drugs.

Received November 30, 2022; accepted January 25, 2024. doi:10.1002/cpt.3206

[1]Department of Pharmacology, Toxicology and Pharmacovigilance, Centre Hospitalier Universitaire de Limoges, Limoges, France; [2]Pharmacology & Transplantation, Institut National de la Santé et de la Recherche Médicale U1248, Université de Limoges, Limoges, France; [3]Fédération Hospitalo-Universitaire SUrvival oPtimization in ORgan Transplantation (FHU SUPORT), Limoges, France; [4]Department of Nephrology, Dialysis and Transplantation, Centre Hospitalier Universitaire de Limoges, Limoges, France; [5]Department of Nephrology, Transplantation, Dialysis, Centre Hospitalier Universitaire Pellegrin, Bordeaux, France; [6]Centre National de la Recherche Scientifique, UMR 5164 Immuno ConcEpT, Bordeaux University, Bordeaux, France; [7]Department of Nephrology and Kidney Transplantation, University Hospital of Amiens, Amiens, France; [8]Service de Néphrologie, Rouen University Hospital, Rouen, France; [9]Department of Nephrology and Organ Transplantation, Centre Hospitalier Universitaire de Toulouse, Toulouse, France; [10]Université Paul Sabatier, Toulouse, France; [11]Institut National de la Santé et de la Recherche Médicale, U1043, IFR-BMT, Centre Hospitalier Universitaire Purpan, Toulouse, France; [12]Department of Nephrology and Kidney Transplantation, University Hospital of Tours, Tours, France; [13]François Rabelais University, Tours, France; [14]Department of Nephrology, Dialysis and Transplantation, Centre Hospitalier Universitaire de Poitiers, Tours, France. *Correspondence: Pierre Marquet (pierre.marquet@unilim.fr)

† These authors contributed equally.

Mycophenolic acid is given to most kidney transplant recipients (KTRs), mainly as an adjunct to first-line drugs due to its suboptimal benefit–risk balance at the recommended doses. Summaries of product characteristics still propose standard doses in adults, despite huge between-patient pharmacokinetic variability[1] and abundant evidence of an exposure–efficacy relationship.[2–4]

The pharmacokinetics (PK) of mycophenolic acid, the active compound of mycophenolate drugs, is complex due to nonlinear absorption; phase II hepatic metabolism by polymorphic metabolic enzymes; biliary excretion and enterohepatic circulation of the active substance involving polymorphic membrane transporters; high plasma protein binding; renal elimination of the metabolites; and drug–drug interactions.[5] This may explain why mycophenolic acid concentrations at single timepoints do not efficiently predict patient outcomes, whereas the inter-dose area under the curve (AUC_{0-12h}) does.[2,6–9] Consequently, many groups developed limited sampling strategies (LSSs) to estimate mycophenolic acid AUC_{0-12h}.[1]

Four randomized clinical trials (RCTs) compared fixed dosing vs. concentration-controlled dosing of mycophenolate mofetil over the first year post transplantation.[10–13] Two used a therapeutic drug monitoring (TDM) strategy,[10,11] meaning that mycophenolic acid exposure (AUC or C_0) was reported but no dose adjustment was proposed, which meant that the physicians had to decide whether or not and by how much the dose should be changed. The other two trials used an interventional strategy[12,13] in which, with each AUC_{0-12h} estimate, a mycophenolate mofetil dose (or dose range) was recommended to reach a predefined target (or target range). Exposure measurement with individual dose recommendation, but not "simple" TDM, led to effective control of mycophenolic acid exposure and better clinical outcomes than fixed dose mycophenolate mofetil.[3] The difference probably lies in the proportion of patients in whom the dose adjustments required were made (e.g., 85% in a positive RCT[12] as compared with only 48% in a negative RCT[10]).

Based on the positive results we obtained with one of these interventional dose adjustment trials[12] we developed several population PK models and Bayesian estimators for mycophenolate mofetil in various transplantation settings.[14–17] In 2005, we launched the ISBA expert system (Immunosuppressive Bayesian Dose Adjustment, https://abis.chu-limoges.fr/login), a free online expert system offering AUC estimation and model-informed dose recommendations for different immunosuppressive drugs, including mycophenolate mofetil. Over the past 18 years, ~100,000 model-informed precision dosing (MIPD) requests have been received for mycophenolate mofetil (about half from France), for ~72,000 adult KTRs. Retrospective analyses of the results from the first 7,000 adult and 1,000 pediatric KTRs, respectively, showed that when the dose recommended using mycophenolate mofetil MIPD was actually prescribed, the subsequent AUC was significantly more often in the recommended AUC range and the interindividual AUC variability was systematically lower, at all post-transplantation periods.[18,19]

The main objective of the present retrospective, observational study nested in two prospective cohorts of adult KTRs was to evaluate rejection-free survival and the cumulative incidences of graft rejection and adverse effects at 3 years post transplantation in patients who had mycophenolate mofetil MIPD in a routine setting, as compared with those who did not. Secondary objectives were to compare rejection-free survival and the cumulative incidence of graft rejection between patients with MIPD or not, sorted by risk of graft rejection or associated calcineurin inhibitor (CNI).

METHODS

Design and study population

We analyzed data collected prospectively in adult *de novo* KTRs who provided written informed consent to participate in two successive cohort studies in France.

The kidney transplant epidemiology study EPIGREN aimed at evaluating the feasibility, efficacy and acceptability of various tools to collect clinical data and patient-reported outcomes (PROs) in all adult KTRs receiving immunosuppressive drugs. The protocol and the other objectives have been previously described[20–23] and are detailed in **Supplementary Material**. Donor human leukocyte antigen (HLA) characteristics, recipient biographic, baseline clinical and lab test data were collected at inclusion. Clinical and pharmacological data were collected during post-transplant hospitalization and then at protocol visits at Months 1 (M1), M3, M6, M9, M12, M18, M24, M36, and M48. A total of 444 patients were recruited prospectively between 2007 and 2011, 7 were lost to follow-up, and 3 withdrew their consent.

Using the tools selected and validated in EPIGREN, the kidney transplant pharmaco-economic study EPHEGREN was conducted with the primary objective of comparing the pharmaco-economic impact of different immunosuppressive strategies and with several secondary objectives (**Supplementary Material**), in adult KTRs from 7 investigation sites in France followed up using the same visit schedule as EPIGREN. Patients included in EPIGREN were proposed to participate in EPHEGREN, and 184 of them accepted.

A total of 569 patients transplanted between 2013 and 2017 were included in EPHEGREN and <10% were lost to follow-up. Overall, 2,296 self-administered questionnaires were collected.

Importantly, mycophenolate mofetil model-informed precision dosing was neither planned nor organized in either cohort study.

These cohorts were sponsored by Limoges University Hospital and complied with the Declaration of Helsinki. They were approved and authorized by the regional Ethics Committee (n°06-040 on 05/19/2006 for EPIGREN and n°130-2013-30 on November 20, 2013, for

EPHEGREN), the French Medicine Agency (n°060566 on 08/08/2006) and the National Committee for Informatics and Liberties (907275 ACT in 2006 for EPIGREN, 912242 ACT in 2012 for EPHEGREN).

Inclusion criteria

For both cohorts, all *de novo* transplant patients were eligible, except if they did not understand the protocol, were not able to read and understand French, or could not be followed in one of the investigating centers. The patients retained in the present post hoc study were those included in either cohort in the first month post transplantation and who received a mycophenolate drug (either mycophenolate mofetil or enteric-coated mycophenolate sodium). Sixteen patients who had MIPD for tacrolimus or cyclosporine were excluded.

Mycophenolate mofetil MIPD procedure

Since this study was made possible by linking the ISBA database with the EPIGREN/EPHEGREN databases, the only patients considered for the MIPD group were those registered in the ISBA expert system (which is used by most kidney transplant centers throughout France) at the time of their participation in either of the cohort studies. Following ISBA requirements, patients had to be on mycophenolate mofetil (and not enteric-coated mycophenolate sodium) and the mycophenolic acid plasma concentration had to be measured locally at 20 minutes, 1 hour, and 3 hours post dosing. Mycophenolic acid inter-dose AUC was estimated using a three-point LSS (20 minutes, 1 hour, and 3 hours post dosing), population PK models and maximum *a posteriori* Bayesian estimators adapted to early/late post-transplant periods and the associated calcineurin inhibitor. The expert system proposes mycophenolate mofetil doses to reach an AUC_{0-12h} of 45 mg.h/L. Whether this recommended dose was actually prescribed was assessed approximately as previously reported,[18,19] by comparing it to the dose received by the patient at the next mycophenolate mofetil MIPD request, whatever the time interval might be between the two.

Data collection

At each study visit, clinical data and laboratory test results were retrieved from medical records and the patients were invited to fill in a self-administered questionnaire. All the rejection episodes were collected, whether from protocol or for-cause biopsies, without further categorization in the EPIGREN cohort, whereas in EPHEGREN rejection was categorized as antibody-mediated (AbMR), T-cell mediated (TCMR), or mixed rejection as per local pathologist assessment. The PROs included self-reported adverse events (AEs) using a dedicated list set up by pharmacologists and transplant physicians. Maintenance immunosuppressive drugs and all their routine trough blood concentrations were also collected prospectively, but not mycophenolate mofetil AUC values when measured since they were not planned or used in the cohort studies.

Patients received different induction therapies, classified in three groups to categorize their "strength" (basiliximab as category 1, anti-thymocyte globulins as category 2, and rituximab or IV polyclonal immunoglobulins (IvIg) as category 3). Since several transplantation centers participating in EPIGREN or EPHEGREN were ISBA users, either for all their patients at regular intervals or for complicated cases only, and mainly for mycophenolate mofetil (**Figure 1**), we recently linked the ISBA database with EPIGREN/EPHEGREN, identified patients with mycophenolate mofetil MIPD during their participation in either of the cohort and retrieved information about post-transplantation time, associated immunosuppressants, mycophenolate mofetil dose received, mycophenolic acid AUC_{0-12h}, and recommended dose adjustment.

Statistical analysis

Statistical analysis was performed using R version 4.1.0 (R Foundation). Categorical data are reported as frequencies or percentages, and continuous data as median and interquartile range. Comparisons were made using the Pearson χ^2 test for categorical data, and the Kruskal–Wallis test for continuous data. Bonferroni risk correction was applied to multiple comparisons.

The cumulative incidence of rejection was compared between study arms using the Andersen-Gill model, an extension of the Cox proportional hazard model for recurrent events. Two-sided P values <0.05 were considered statistically significant.

The time to the first rejection episode was compared between the MIPD and control groups using Cox modeling to compute the hazard ratio (HR) with the "survival3.4.0" R package.

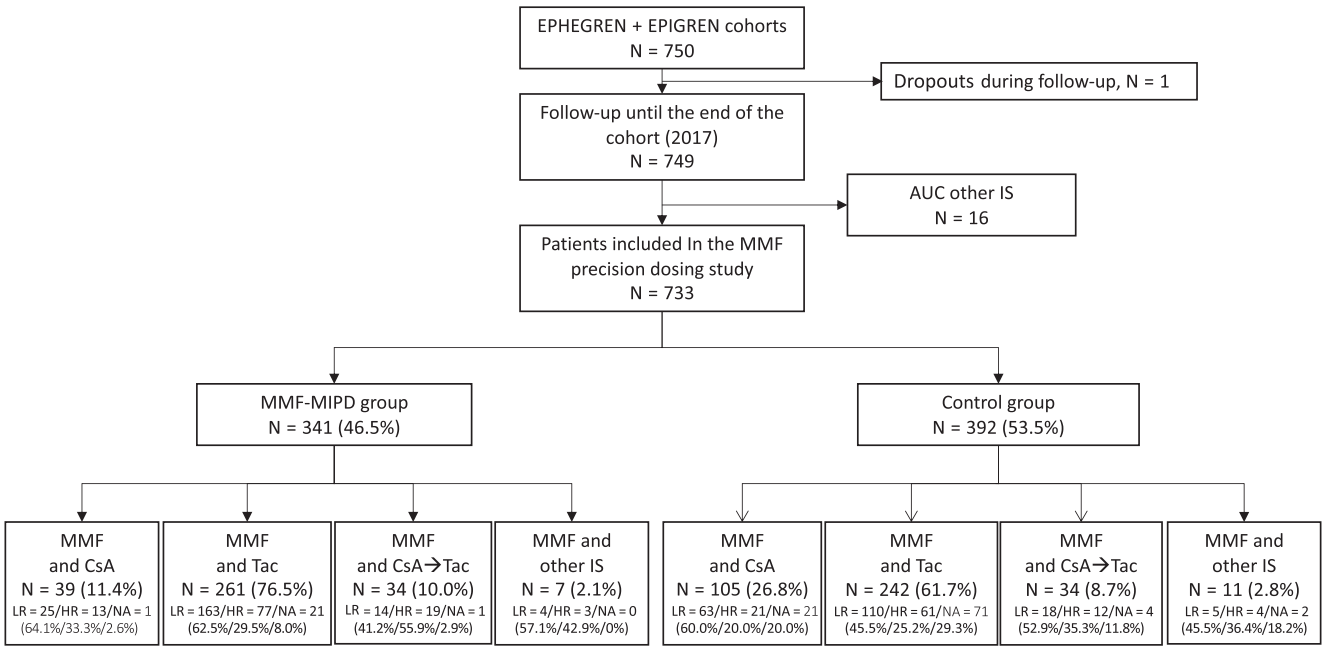

Figure 1 Study flowchart. AUC, area under the curve; CsA, cyclosporine; HR, high-risk stratum; IS, immunosuppressive drug; LR, low-risk stratum; MIPD, model-informed precision dosing; MMF, mycophenolate mofetil; NA, patients with missing data excluded from propensity score analyses; other IS, everolimus/sirolimus; Tac, tacrolimus.

Survival without rejection was then adjusted on factors reported to be associated with rejection (recipient age ≤50 year; donor age ≤50 year; number of HLA mismatches above the median (>5); existence of pretransplant donor-specific antibodies or DSA; cold ischemia time >1,000 minutes; and delayed graft function) using univariate followed by multivariate Cox modeling with upward and backward stepwise selection based on the Akaike information criterion. The robustness of the results was assessed by 1,000 bootstraps followed by 1,000 upward-backward selection steps.

To compute a quantitative propensity score of graft rejection for each patient, the potential determinants of rejection (except those possibly concomitant or consecutive to rejection) were also included in a generalized linear model followed by backward stepwise selection. For pretransplant DSA and *de novo* DSA, the few missing data were imputed as "absent," according to the concept most common attribute value fitting (CMCF). Patients with missing data for the other significant covariates were excluded from propensity score analyses.

A second robustness analysis was performed using a stronger propensity score, computed in the same way but in the subgroup of patients transplanted after December 31, 2009, when pretransplant immunization, graft incompatibility rate (the French equivalent of cPRA%), and HLA incompatibilities were reported in most medical records and could also be accounted for. Patients with missing cPRA% were excluded, and missing data for the other covariates were handled as explained above.

With each propensity score, patients were stratified into two subsets of high or low risk of graft rejection based on the score distribution if subgroups showed up, or otherwise on the median.[24]

RESULTS

Study cohort

The eligibility criteria were met for 733 patients: The exposed group included 341 patients in whom mycophenolate mofetil MIPD was performed (1,049 AUCs in total) and the control group 392 patients who had no mycophenolic acid AUC_{0-12h} retrieved from the ISBA database (**Figure 1**). In the control group at inclusion, 42% of the patients were on enteric-coated mycophenolate sodium and 58% on mycophenolate mofetil, as compared with 2% and 98% in the mycophenolate mofetil MIPD group (**Table S1**). The 17 patients who had a rejection episode before their first mycophenolate mofetil MIPD were included in the control group since survival analysis considers only the first episode. Moreover, none of these 17 patients had a second rejection episode, so they were also kept in the control group for cumulative incidence analysis. In the MIPD group, 82.1% of the patients had their first AUC measurement (by definition before any rejection episode) between 1 week and 3 months post transplantation, with differences between investigation centers (**Figure S1**). The number and dispersion of mycophenolate mofetil AUC values decreased over time (**Figure S2**). The dose adjustments proposed are shown in **Figure S3**. Among the 216 patients who had at least two AUCs (**Table S2**), the dose received on the second instance matched the dose recommended on the first in 166 patients (76.9%), decreasing from 82.1% if the two AUC estimations were <1 month apart to 61.1% if they were >12 months apart (**Figure S4**). Despite this very high application rate, the average dose (converted to mycophenolate mofetil equivalent for patients on enteric-coated mycophenolate sodium) was numerically lower in the MIPD group at all study periods starting at M1, and significantly so at M18 (**Table S4**).

The main socio-demographic and clinical characteristics of the population are shown in **Table 1**. The CNI combined with mycophenolate mofetil was tacrolimus (261 MIPD patients and 242 controls), cyclosporine (39 and 105 patients, respectively), or cyclosporine switched to tacrolimus (34 in each group) (**Figure 1** and **Table 1**). The percentage of patients on induction therapy with basiliximab was higher in the MIPD group, and the percentage of patients on anti-thymoglobulins, IvIg, or rituximab was higher in the control group. In contrast, tacrolimus maintenance therapy was more frequent in the MIPD and cyclosporin in the control group. Tacrolimus C_0 and cyclosporin C_0 were not different between groups (**Table S3**). The average mycophenolate mofetil doses given at the different protocol visits were slightly, and at M18 significantly, lower in the MIPD group (**Table S4**).

Fourteen MIPD patients died and 13 returned to dialysis, as compared with respectively 15 and 20 controls ($P = 0.847$ and 0.401). Over the first 3 years (1,096 days) post transplantation, 154 rejection episodes were reported for 113 patients (37 MIPDs and 76 controls), among whom 25 had >1 episode (10 and 15 patients, respectively). The rejection episodes reported in EPHEGREN were AbMR (12 MIPDs vs. 14 controls), TCMR (12 vs. 21), or mixed rejection (1 vs. 3).

Impact of mycophenolate mofetil MIPD on graft rejection

Rejection-free survival at 3 years was 91.2% in the MIPD group and 80.6% in controls (HR = 0.40 (0.26, 0.60), $P < 0.001$, **Figure 2a**). Multivariate Cox analysis confirmed that rejection-free survival was strongly associated with mycophenolate mofetil MIPD (HR = 0.45 (0.28, 0.72), $P = 0.001$), when adjusted for: the number of HLA mismatches, *de novo* DSA, and corticosteroids after 6 months, favoring rejection; the number of study visits attended, and induction treatment strength, protective against rejection (**Table 2**).

The cumulative incidence of graft rejection over the first 3 years was 2.5-fold lower in the MIPD than in the control group (5.08% vs. 12.7% per patient × year, respectively), corresponding to HR = 0.49 (0.34, 0.71), $P < 0.001$ (**Figure 2d**).

A sensitivity survival analysis was performed after exclusion of all the patients on enteric-coated mycophenolate sodium at any time during their participation in the study, showing a similar difference between groups (HR = 0.34 (0.21, 0.57), $P < 0.001$, **Figure S5**).

Survival without rejection beyond the first year post transplant in the study population was numerically lower in the MIPD group overall and in each of the MIPD propensity subgroups, but this was not statistically significant, probably due to small event numbers (**Figure S6**).

Subgroup analysis depending on the type of rejection. Kaplan-Meyer analysis showed numerically better TCMR-free (HR = 0.53 (0.26, 1.09), $P = 0.085$) or AbMR-free (HR = 0.62 (0.28, 1.35), $P = 0.229$) survival over 3 years in the MIPD group, but these differences were not significant. Similar tendencies were found in the two propensity score classes.

Table 1 Characteristics and outcomes of the patients included in the study (*N* = 733)

	Control group	MMF MIPD group	*P*
Patient number	392	341	
Transplantation center (%)			**<0.001**[a]
Amiens	68 (17.3)	33 (9.7)	
Bordeaux	172 (43.9)	106 (31.1)	
Limoges	26 (6.6)	108 (31.7)	
Poitiers	2 (0.5)	1 (0.3)	
Rouen	8 (2.0)	88 (25.8)	
Toulouse	95 (24.2)	5 (1.5)	
Tours	21 (5.4)	0 (0)	
Men, No. (%)	245 (62.5)	234 (68.6)	0.082
Recipient age, median (IQR)	54 (44–63)	54 (45–63)	0.952
Donor age, median (IQR)	54 (43–65)	54 (43–64)	0.578
Number of HLA mismatches, median (IQR)	5 (4–6)	5 (4–6)	0.923
Graft incompatibility rate (French cPRA), median (IQR)	0 (0–11)	0 (0–30)	0.114
Pretransplant sensitization, yes (%)	92 (30.3)	70 (31.0)	0.861
Pretransplant DSA, yes (%)	23 (5.9)	18 (5.3)	0.725
Pretransplant hypertension, yes (%)	342 (95.0)	299 (91.4)	0.062
Pretransplant diabetes, yes (%)	48 (17.2)	53 (17.9)	0.825
Cold ischemia time, median (IQR)	822 (632–1,062)	897 (687–1,118)	**0.036**
Rank of kidney transplantation (%)			0.326
0	338 (86.2)	289 (84.8)	
1	48 (12.2)	50 (14.7)	
2	6 (1.5)	2 (0.6)	
Delayed graft function, yes (%)	25 (6.4)	40 (11.7)	**0.011**
MCS-QOL[b] <40(%)	115 (37.8)	110 (36.3)	0.697
PCS-QOL[c] <40 (%)	121 (39.9)	122 (40.1)	0.960
De novo DSA, yes (%)	42 (12.6)	35 (11.6)	0.704
Rejection episodes, No. (%)	76 (19.4)	37 (10.9)	**0.001**
Rejection episodes censored at 3 years, No. (%)	76 (19.4)	31 (9.1)	**<0.001**
Deaths	15 (3.8)	14 (4.1)	0.847
Return to dialysis	20 (5.1)	13 (3.8)	0.401
No. Study visits, median (IQR)	4.00 (4.00–6.00)	6.00 (5.00–7.00)	**<0.001**
Living donor (%)	38 (12.1)	37 (11.0)	0.685
Induction treatment category (%)			**0.001**
1: basiliximab	257 (65.6%)	265 (77.7%)	
2: anti-thymoglobulins	117 (29.8%)	66 (19.4%)	
3: rituximab, IVIg	18 (4.6%)	10 (2.9%)	

DSA, donor-specific antibodies; HLA, human leukocyte antigen; IVIg, intravenous immunoglobulin; IQR, interquartile range; MIPD, model-informed precision dosing; MMF, mycophenolate mofetil.
[a]The corrected *P* significance threshold was fixed at 0.0025 to account for multiple testing. [b]MCS-QOL: mental component score of the SF36 quality-of-life questionnaire. [c]PCS-QOL: physical component score of the SF36 quality-of-life questionnaire.

Subgroup analysis depending on the associated CNI. Among the patients on tacrolimus, those in the MIPD group presented, in general, significantly better rejection-free survival than those in the control group ($n = 503$, HR = 0.35 (0.20, 0.61), $P < 0.001$, **Figure 3a**) and when at low risk of rejection ($n = 273$, HR = 0.42 (0.18, 0.94), $P = 0.036$, **Figure 3b**), but it was not significant in those at high risk of rejection ($n = 138$, HR = 0.38 (0.14, 1.04), $P = 0.059$, **Figure 3c**). In patients on cyclosporine, mycophenolate mofetil MIPD led to numerically but not significantly better rejection-free survival, overall ($n = 144$, HR = 0.58 (0.25, 1.34), $P = 0.205$, **Figure 3d**) and in the two risk subclasses (**Figure 3e,f**), probably because of small numbers. In the patients who switched from cyclosporine to tacrolimus ($n = 68$), there was no difference in rejection-free survival between groups, globally (HR = 1.04

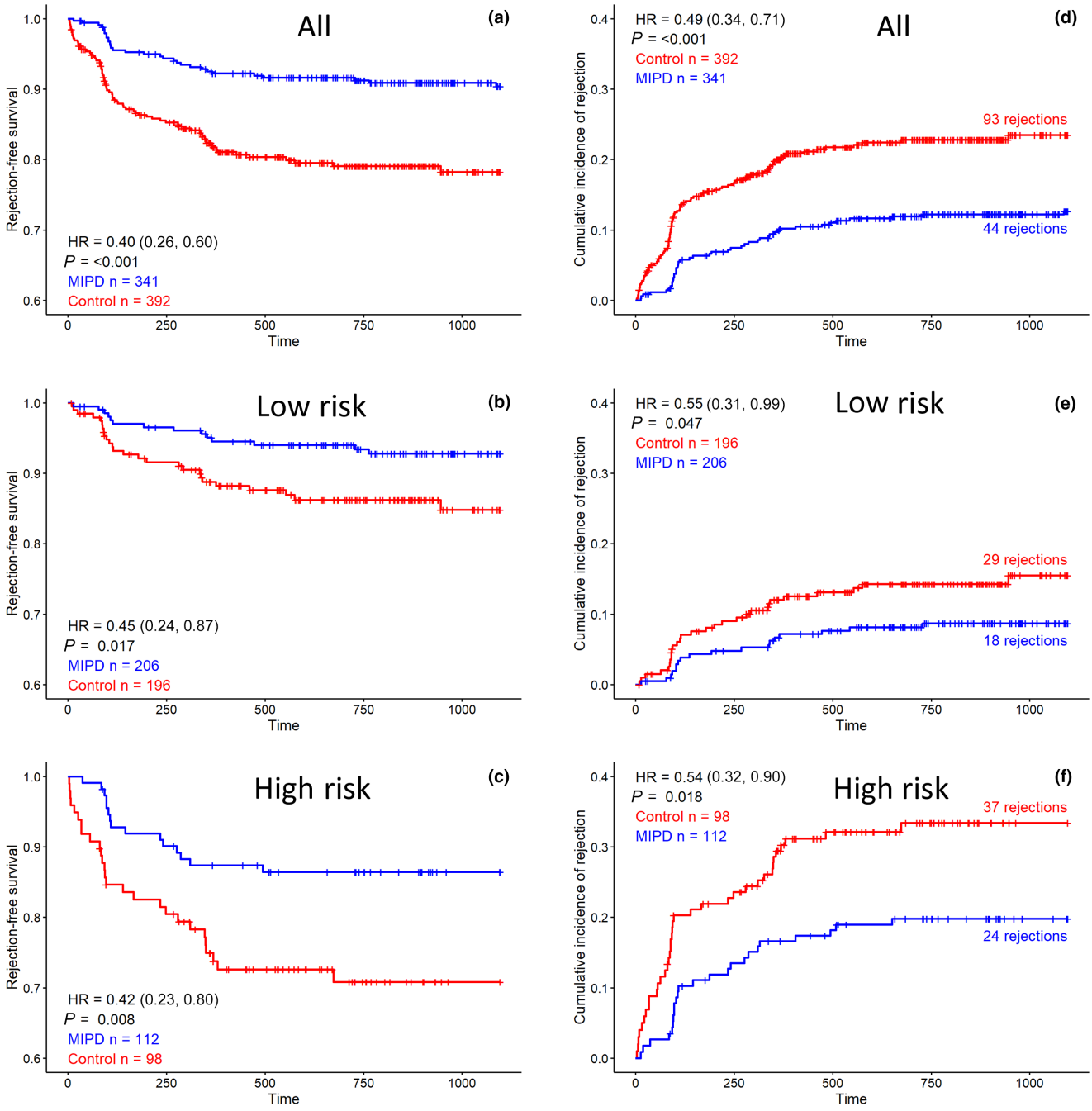

Figure 2 Kaplan–Meier curves of rejection-free survival (**a**) in the MMF model-informed precision dosing (MIPD) group vs. control group, (**b**) in the low-risk propensity score subclass and (**c**) in the high-risk propensity score subclass. Cumulative incidence of rejection (**d**) in the MIPD vs. control group, (**e**) in the low-risk propensity score subclass and (**f**) in the high-risk propensity score subclass. HR, hazard ratio: MIPD, model-informed precision dosing.

(0.34, 3.24), $P = 0.941$) or in the high-risk (HR = 1.15 (0.27, 4.81), $P = 0.849$) and low-risk (HR = 0.41 (0.04, 3.98), $P = 0.444$) subclasses.

Propensity score and stratified analysis. HLA mismatches and pretransplant DSA[25–27] were considered in the calculation of the individual propensity score, for all the patients without missing data ($n = 612$, 83.5% of the study population). *De novo* DSA and the use of corticosteroids after the 6th month post transplantation were not considered, because the first can be concomitant, and the second consecutive, to graft rejection. Center effect, cold ischemia time >1,000 min, delayed graft function and the number of study visits attended were not significant. Based on their individual propensity score calculated using donor age <50 years, recipient age <50 years, number of HLA mismatches, pretransplant DSA, and induction therapy strength, two subsets were identified on the score distribution: patients at high risk ($n = 210$) or low risk ($n = 402$) of rejection.

Table 2 Univariate and multivariate Cox analyses of the association of rejection-free survival and potential risk factors over the first 3 years post transplantation

	Univariate analysis			Multivariate analysis			
	HR	IC95%	*P* value	HR	95%CI	*P* value	% Bootstrap selection
Transplantation center			>0.9				
Men, No.	0.95	0.64, 1.40	0.782				
Donor age < 50 years, yes	0.86	0.55, 1.34	0.500				
Recipient age < 50 years, yes	1.25	0.85, 1.83	0.252				
Number of HLA mismatches	1.22	1.05, 1.41	**0.008**	1.18	(1.02, 1.37)	**0.030**	80.3
Graft incompatibility rate (French cPRA)	1.00	0.99, 1.01	0.612				
Pretransplant sensitization, yes	0.79	0.48, 1.30	0.350				
Rank of kidney transplantation, >1 vs. 1	0.95	0.55, 1.63	0.843				
Pretransplant hypertension, yes	1.00	0.47, 2.16	0.992				
Pretransplant diabetes, yes	0.73	0.39, 1.36	0.324				
Pretransplant DSA, yes	1.39	0.68, 2.86	0.367				
Cold ischemia time > 1,000, yes	0.73	0.46, 1.15	**0.169**	Not kept in the final model			
Increasing induction treatment strength	0.71	0.47, 1.05	**0.089**	0.51	(0.32, 0.84)	**0.007**	94.2
No. study visits	0.81	0.72, 0.92 91i2	**0.001**	0.88	(0.74, 1.05)	0.153	50.2
Delayed graft function, yes	0.83	0.40, 1.71	0.615				
De novo DSA, yes	2.51	1.59, 3.95	**<0.001**	2.38	(1.44, 3.95)	**0.001**	96.1
Corticosteroids after M6, yes	3.55	2.12, 5.97	**<0.001**	4.77	(2.53, 9.00)	**<0.001**	100
MMF MIPD, yes	0.40	0.26, 0.60	**<0.001**	0.45	(0.28, 0.72)	**0.001**	97.2
First-line ISD (vs. tacrolimus							
Cyclosporine	2.16	1.41, 3.30	**<0.001**	Not kept in the final model			
Switched CsA➔Tac	1.49	0.80, 2.77	0.212				
Others	1.57	0.49, 5.00	0.449				
MMF maintenance dose (per milligram increase)							
M1	1.0002	0.9997, 1.0006	0.477				
M3	1.0001	0.9997, 1.0005	0.727				
M6	0.9999	0.9995, 1.0003	0.519				
M12	0.9999	0.9994, 1.0003	0.560				
M18	1.0001	0.9996, 1.0006	0.705				
M24	1.0001	0.9996, 1.0006	0.801				
M30	1.0000	0.9994, 1.0005	0.879				
M36	0.9998	0.9991, 1.0005	0.596				
CNI exposure							
Tacrolimus C0 (per ng/mL increase)							
M1	1.05	0.98, 1.12	0.182				
M3	1.01	0.92, 1.11	0.760				
M6	1.09	0.98, 1.22	0.105				
M12	1.10	0.90, 1.35	0.343				

(Continued)

Table 2 (Continued)

	Univariate analysis			Multivariate analysis			
	HR	IC95%	*P* value	HR	95%CI	*P* value	% Bootstrap selection
M18	0.78	0.51, 1.18	0.237				
M24	0.91	0.54, 1.52	0.717				
M30	0.89	0.54, 1.47	0.647				
M36	1.03	0.79, 1.33	0.845				
Cyclosporine C0 (per ng/mL increase)							
M1	1.00	0.99, 1.00	0.389				
M3	1.00	0.99, 1.00	0.407				
M6	1.00	1.00, 1.01	0.599				
M12	1.00	0.98, 1.01	0.776				
M18	1.01	1.00, 1.02	0.032				
M24	1.00	0.98, 1.02	0.954				
M30	1.02	0.98, 1.05	0.332				
M36	1.01	0.98, 1.03	0.539				

C0, predose blood concentration; CNI, calcineurin inhibitor; CsA, cyclosporine; DSA, Donor-specific antibodies; HLA, human leukocyte antigen; HR, hazard ratio; 95%CI, 95% confidence interval; ISD, immunosuppressive drugs; M, month; MIPD, model-informed precision dosing; MMF, mycophenolate mofetil; NA, not assessed (due to the absence or the very low number of rejection episodes at the corresponding visit); Tac, tacrolimus.

The risk level could not be assessed in 121 patients due to missing data (**Figure 1**). Better rejection-free survival in the mycophenolate mofetil MIPD group was confirmed in these two propensity score groups (HR = 0.42 (0.23, 0.80)), $P = 0.008$ and HR = 0.45 (0.24, 0.87), $P = 0.017$ for the high- and low-risk groups, respectively, **Figure 2b,c**). The MIPD group showed a cumulative incidence of rejection 2.0-fold lower (3.56% vs. 6.95% per patient × year; HR = 0.55 (0.31, 0.99), $P = 0.047$) and 2.3-fold lower (8.36% vs. 19.2% per patient × year; HR = 0.54 (0.32, 0.90), $P = 0.018$) in the low-risk and high-risk groups, respectively (**Figure 2e,f**).

The graft incompatibility rate (French equivalent of cPRA%) and pretransplant immunization were available for 530 patients (72%) transplanted after December 31, 2009 (**Figure S7**). These risk factors were combined with those selected above to calculate a more robust propensity score in a final population subset of 422 patients (57.6%), after exclusion of those with missing cPRA% (**Table 3**). Mycophenolate mofetil MIPD was associated with better rejection-free survival in the low-risk class ($n = 267$, HR = 0.40 (0.17, 0.90), $P = 0.028$), but not in the high-risk one ($n = 155$, HR = 0.57 (0.27, 1.17), $P = 0.124$). The results were similar for the cumulative incidence of rejection (**Figure S8**).

Mycophenolic acid MIPD and adverse events

Compared with the 392 controls, the 341 mycophenolate mofetil MIPD patients had more frequent anemia (188 vs. 166 AEs, respectively; $P = 0.003$); leukopenia (70 vs. 47; $P = 0.004$); gastrointestinal AEs (329 vs. 216; $P < 0.001$); nonviral infections (387 vs. 344; respectively; $P < 0.001$); patient-reported diarrhea (387 vs. 315; $P < 0.001$); nausea (156 vs. 107; $P < 0.001$); and constipation (189 vs. 133; $P < 0.001$; **Table 4** and **Figure S9**). No difference was found for cytomegalovirus (CMV) infections or other virus infections. More importantly, in the mycophenolate mofetil MIPD group many of these AEs were reported before the first mycophenolic acid AUC estimation (76% of anemia, 39% of leucopenia, 44% of CMV infection, 39% of other viral infection, 43% of nonviral infection cases, and 54% of gastrointestinal AEs) (**Figure S8**).

DISCUSSION

This observational study nested in a cohort (with very permissive inclusion criteria) of 733 KTRs in a real-life setting shows that mycophenolate mofetil MIPD based on mycophenolic acid AUC_{0-12h} was associated with significantly better 3-year survival without graft rejection, and significantly lower cumulated incidence of rejection episodes. Although no causality can be inferred from an observational study, this association was consistent in patients with a low or high risk of rejection (with a larger quantitative effect in those at high risk, as previously reported[25]), and in patients on tacrolimus. A previous randomized clinical trial[12] demonstrated such causality, but it was limited to patients with low to mild risk of rejection, on cyclosporin, and followed up over only 1 year post transplant. In the present study, mycophenolate mofetil MIPD was not associated with a lower cumulative incidence of rejection in patients on cyclosporine, whether at low risk or high risk of rejection, but they only represented 13% of the MIPD group, leading to low statistical power. Still, mycophenolate mofetil MIPD resulted in similar and clinically significant reductions of the cumulated incidence of graft rejection, in the above-mentioned randomized trial as well as in the present observational study (68.7% at 1 year and 60.0% at 3 years, respectively).[12] The observational design may even have disadvantaged MIPD here, since some patients in the control group might also have had mycophenolate mofetil MIPD (or TDM) using local LSS and calculators, or mycophenolate mofetil C_0, while a few others had mycophenolate mofetil MIPD

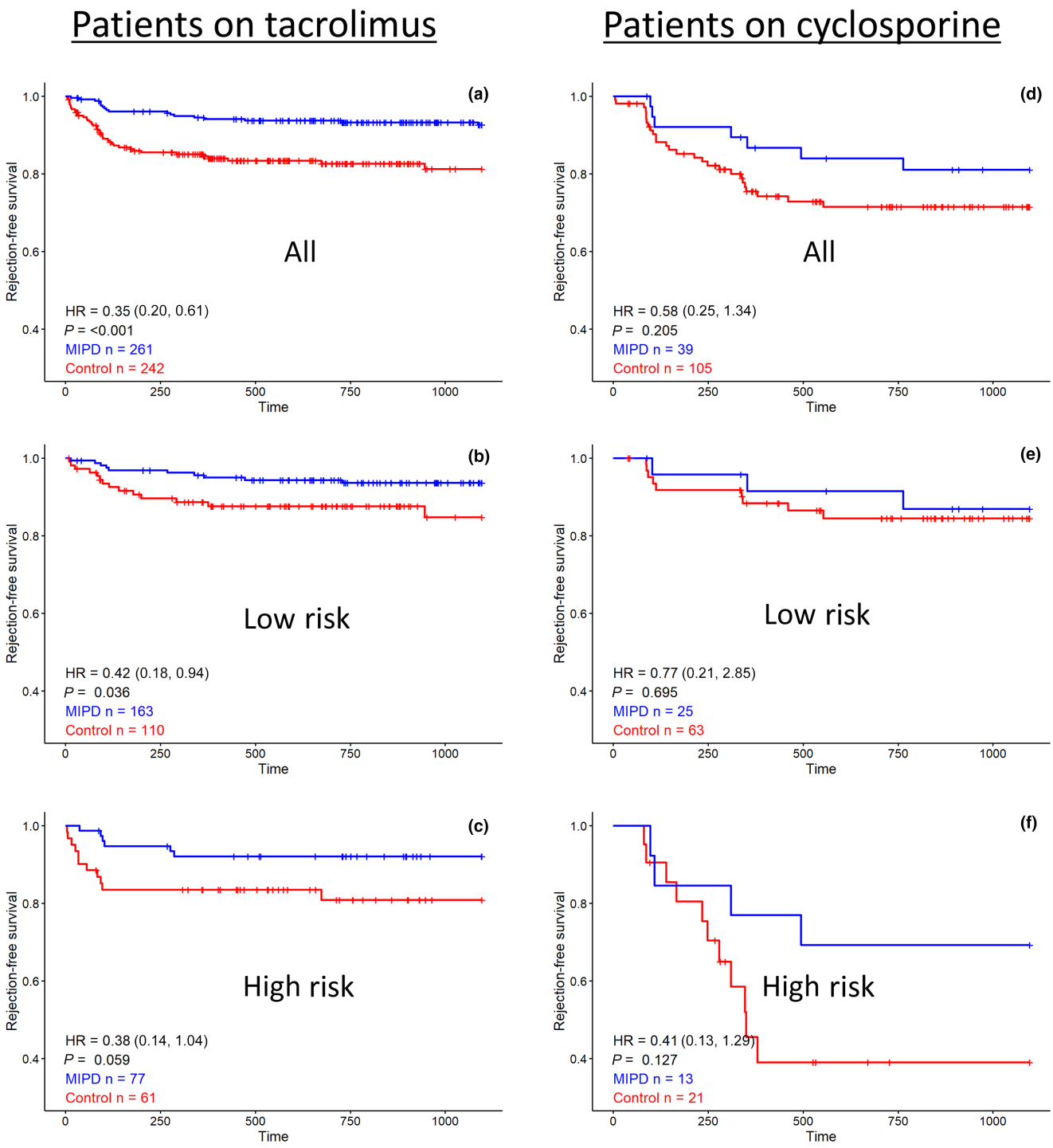

Figure 3 Kaplan–Meier curves of rejection-free survival (**a**) in the MIPD vs. control group in patients on tacrolimus; (**b**) in the low-risk propensity score subclass; and (**c**) in the high-risk propensity score subclass. Kaplan–Meier curves of rejection-free survival (**d**) in the MIPD group vs. controls in patients on cyclosporine; (**e**) in the low-risk propensity score subclass; and (**f**) in the high-risk propensity score subclass. HR, hazard ratio: MIPD, model-informed precision dosing.

even though they were apparently on enteric-coated mycophenolate sodium (**Supplementary Results** and **Table S1**).

Although not planned or checked as part of the EPIGREN and EPHEGREN study protocols, 77% of the mycophenolate mofetil dose recommendations made based on mycophenolic acid AUC_{0-12h} were applied by the physicians, as inferred from the dose received by the patients at the next AUC estimation request (up to >1 year later) (**Figure S4**). Perfect dose matching cannot be expected, since mycophenolate mofetil dose increase may be limited by toxicity and dose decrease by history of rejection, or in the context of CNI exposure minimization, for instance. In a large retrospective analysis of more than 7,000

Table 3 Robustness of rejection-free survival analysis using two modes of propensity score calculation

				Rejection-free survival analysis		
		Control group	MIPD group	HR	95%CI	*P*
Propensity score including donor age <50 years, recipient age <50 years, HLA mismatch, pre-transplant DSA, and induction therapy strength	Low-risk propensity score subclass	196	206	0.45	(0.24, 0.87)	0.017
	High-risk propensity score subclass	98	112	0.42	(0.23, 0.80)	0.008
Stronger propensity score also including graft incompatibility rate (cPRA%) and pretransplant sensitization	Low-risk propensity score subclass	143	124	0.40	(0.17, 0.90)	0.028
	High-risk propensity score subclass	78	77	0.57	(0.27, 1.17)	0.124

Robustness of rejection-free survival analysis using two modes of propensity score calculation: one including only 5 pretransplant risk factors (83.5% of the study population) vs. 7 pre-transplant risk factors (only in patients transplanted in 2010 and later, 57.6% of the study population).
DSA, HLA; human leukocyte antigen; HR, hazard ratio; 95%CI, 95% confidence interval; MIPD, model-informed precision dosing.

Table 4 Number of adverse events in the mycophenolate mofetil model-informed precision dosing group (all modalities) vs. the control group

	Number of AEs				MIPD group (*n* = 341)	
	Control group (*n* = 392)	MIPD group (*n* = 341)				
AE	Reported during the full follow-up (up to 3 years)		Cumulative incidence HR (IC95%)	*P*	Reported before The 1st MMF MIPD *N* (%)	Reported after
Anemia	166	188	1.37 (1.11, 1.69)	0.003	142 (75.5)	46 (24.5)
Leukopenia	47	70	1.73 (1.19, 2.50)	0.0041	27 (38.6)	43 (61.4)
Gastrointestinal adverse events	216	329	1.83 (1.54, 2.17)	<0.001	178 (54.1)	151 (45.9)
CMV infections	52	48	1.06 (0.72, 1.57)	0.775	21 (43.8)	27 (56.2)
Other viral infections	57	65	1.31 (0.92, 1.87)	0.133	25 (38.5)	40 (61.5)
Nonviral infections	344	387	1.31 (1.13, 1.68)	<0.001	165 (42.6)	222 (57.4)
Diarrhea[a]	315	387	1.44 (1.24, 1.68)	<0.001		NA
Nausea[a]	107	156	1.70 (1.33, 2.17)	<0.001		NA
Constipation[a]	133	189	1.66 (1.33, 2.07)	<0.001		NA

[a]Patient-reported outcomes.
AEs, adverse events; CMV, cytomegalovirus; HR, hazard ratio; IC95%, concentration of drug producing 95% inhibition; MIPD, model-informed precision dosing; MMF, mycophenolate mofetil; NA, not assessed.

KTRs addressed by 53 different transplantation centers to ISBA for mycophenolate mofetil dose adjustment,[18] 65–78% of the proposed dose adjustments were apparently applied by the clinicians, using the same proxy. In our previous RCT,[12] as well as in another one where a research version of ISBA was used for mycophenolate mofetil dose adjustment,[13] dose matching was 85% and >70%, respectively,[10] whereas it was only 48% in a larger (and negative) RCT of mycophenolic acid AUC monitoring.[10] In an RCT using mycophenolate mofetil TDM based on trough levels,[11] the authors reported "a reluctance to adhere to target mycophenolic acid trough levels … resulting in little differentiation in mycophenolic acid exposure among groups with or without dose adjustment." This confirms the efficacy of mycophenolate mofetil MIPD as opposed to mycophenolate mofetil TDM, which probably results from the combination of (accurate) mycophenolic acid AUC estimation and calculation of an individually adjusted mycophenolate mofetil dose, systematic validation by trained pharmacologists, and timely reporting (median time of 2 hours). And this even though the average mycophenolate mofetil dose was numerically lower in the MIPD group at all study periods (**Table S4**). The initial dose, left to local practice (the two cohort studies being purely observational in terms of drug dosing), was not recorded. However, although more patients in the control group were initially on tacrolimus, 10% had a mycophenolate mofetil dose >2 g/day at 1 month vs. 5% in the mycophenolate mofetil MIPD group (**Table S4**). This suggests that for patients not initially ordered mycophenolate mofetil MIPD, some physicians prescribed early mycophenolate mofetil doses higher than the standard dose, based on previous evidence that the standard dose is not enough in the early post-transplant period. In the mycophenolate mofetil MIPD group, most patients had had no AUC measured yet at early post-transplant visits (e.g., 274/341 at M1), which resulted in a mixture of patients with or without individual dose adjustment

in this group. Moreover, late ordering of the first mycophenolate mofetil MIPD in a substantial proportion of patients (**Figure S1**), frequently because of adverse effects, has probably resulted in an enrichment of this group with patients requiring (controlled) dose reduction. These observations may explain why there were no significant differences in mycophenolate mofetil doses between the two groups, and suggest that improved efficacy in the mycophenolate mofetil MIPD group is not due to higher doses on average, but rather to providing the best — or better — doses to individuals, not changing the average dose but preventing (for patients systematically and regularly monitored) or correcting (for all the others) underexposure and overexposure and reducing interpatient variability in mycophenolic acid AUC (as suggested graphically by **Figure S2**), and better handling of mycophenolate mofetil AEs.

Our first propensity score, calculated in 83.5% of the study population, accounted for five risk factors, donor age <50 years, recipient age <50 years, number of HLA mismatches, pretransplant DSA, and induction therapy strength, which may be suboptimal to appraise the individual risk. To double check the robustness of our results, we built another generalized linear model including additional risk factors (graft incompatibility rate — equivalent to cPRA% and pretransplant sensitization) available from a smaller population subset (57.6%), and it confirmed a statistically significant difference in survival without rejection between the two study arms in the low-risk but not in the high-risk class (probably due to missing data and small patient numbers, since it is inconsistent with the significant difference found in patients with >5 HLA mismatches, see **Figure S7**). Besides, previous studies reported a higher benefit of mycophenolate mofetil TDM in patients with a higher risk of rejection.[25]

The cumulative incidences of hematologic, gastrointestinal and infectious adverse events were all significantly higher in the mycophenolate mofetil MIPD group, but substantial proportions of these AEs occurred before any mycophenolic acid AUC_{0-12h} estimation, meaning that they were either not linked with, or were the reason for, mycophenolate mofetil MIPD. However, due to the absence of pairing between MIPD and control patients it was not possible to exclude patients with these "early" AEs for comparisons. In our previous randomized clinical trial, we found no difference in the overall incidence of AEs between groups, except for herpes virus infection.[12]

This study has several limitations. Steroids are routinely withdrawn at 6 months post transplantation in France, which is not the case in other countries, and the results obtained here may not be extrapolated to such patients. Also, biopsies were not centrally reassessed, and in the EPIGREN cohort, the type of rejection was not even reported. Moreover, propensity scores only balance measured covariates. If unmeasured covariates are confounders, then they can bias treatment effect estimates.[26] The propensity score method demands a thorough clinical understanding and knowledge of the necessary covariates to be included in a model.[27] We believe we used most of the well-known risk factors of rejection[28–30] as inputs in our propensity scores but cannot exclude missing some or other confounders. For instance, patient nonadherence, the CYP3A5*3 genotype or fast metabolizer phenotype, drug–drug interactions with the CNI, etc. It cannot be excluded either that doctors and centers that use mycophenolate mofetil MIPD, take drug dosing more seriously in general, including for the other immunosuppressants, which may impact the incidence of graft rejection. Also, the reasons for which mycophenolate mofetil MIPD was prescribed on one or multiple occasions or not at all were not recorded in ISBA. In a couple of centers it was obviously protocolized and regular. In the others, some ISBA requests were concomitant with adverse effects or, very rarely, suspected rejection. However, this diversity of situations may be considered to be an added value of real-world data (RWD) over RCT and better reflect mycophenolate mofetil MIPD usages in clinical routine. The same stands for the imbalance of patients on enteric-coated mycophenolate sodium between the two groups, since enteric-coated mycophenolate sodium is not readily suitable to MIPD, which may also influence the formulation chosen by each center. RWD cannot provide the same strength of evidence as RCT, but when such evidence already exists (as is the case for mycophenolate mofetil MIPD[12]) it helps to know whether it is also true in the population that receives the intervention in real-life conditions. Drug MIPD is based on a laboratory test interpreted using a medical device (PK model and Bayesian estimator) and aims at influencing the prescriber's choice of drug dosing. Therefore, the level of evidence required should not be the same as for an innovative drug. The FDA "has begun implementation of the National Evaluation System for health Technology (NEST) to leverage RWD in order to more quickly identify safety problems and to better understand the benefit–risk profile of devices used in clinical care. The US Food and Drug Administration (FDA) believes that, if leveraged correctly, the NEST may also help to reduce the time and cost of generating the types of evidence used to support the marketing authorization of FDA-regulated products and to meet postmarket study and reporting requirements."[31] We believe that the level of evidence provided by our previous, well-conducted RCT and the present, large real-world evidence, is sufficient for wider clinical implementation.

Because the efficacy of mycophenolate mofetil MIPD on rejection-free survival cannot be extrapolated to graft survival, we have set up a nationwide study to test this hypothesis in the approximately 48,000 patients who received a kidney graft in France since 2005 (the year when our ISBA expert system started). By linking the two databases, we have found that ~38% of this cohort was addressed to ISBA at least once for mycophenolate mofetil MIPD, which will provide extraordinary statistical power for this next study.

SUPPORTING INFORMATION

Supplementary information accompanies this paper on the *Clinical Pharmacology & Therapeutics* website (www.cpt-journal.com).

ACKNOWLEDGMENTS

We thank all the investigators and patients of the EPIGREN and EPHEGREN cohort, Hélène Roussel for the coordination of the cohorts, Alexandre Garnier for excellent data-management, and Karen Poole for editing this manuscript.

FUNDING

This study was funded by the French ministry of health ("PHRC interrégional"), INSERM, and the University Hospital of Limoges.

CONFLICT OF INTEREST

Lionel Couzi has received lecture fees from Astellas, Chiesi, Novartis, Sandoz, Ostuka, GSK, and Biotest and has participated in advisory boards for Biotest, Hansa, and Novartis. Nassim Kamar has received speaker fees and participated in advisory boards for Astellas, AstraZeneca, Biotest, CSL Behring, Chiesi, ExeViR, Hansa, Merck Sharp and Dohme, Glasgow Smith Kline, Novartis Pharma, Sanofi, Sandoz, and Takeda. Pierre Marquet has received speaker fees and participated in advisory boards for Astellas, Chiesi, Medincell, Sandoz, and Siemens. The other authors declared no conflict of interest for this work.

AUTHOR CONTRIBUTIONS

P.M., C.V., A.H., and C.M. wrote the manuscript. P.M. designed the research. J.P.R, L.C., P.F.W., I.E., N.K., M.B., and A.T. performed the research. C.V., A.H., M.L., C.M., and P.M. analyzed the data.

1. Bergan, S. *et al*. Personalized therapy for mycophenolate: consensus report by the International Association of Therapeutic Drug Monitoring and Clinical Toxicology. *Ther. Drug Monit.* **43**, 150–200 (2021).
2. van Gelder, T. *et al*. A randomized double-blind, multicenter plasma concentration controlled study of the safety and efficacy of oral mycophenolate mofetil for the prevention of acute rejection after kidney transplantation. *Transplantation* **68**, 261–266 (1999).
3. Metz, D.K. *et al*. Optimizing mycophenolic acid exposure in kidney transplant recipients: time for target concentration intervention. *Transplantation* **103**, 2012–2030 (2019).
4. Meziyerh, S. *et al*. Tacrolimus and mycophenolic acid exposure are associated with biopsy-proven acute rejection: a study to provide evidence for longer-term target ranges. *Clin. Pharmacol. Ther.* **114**, 192–200 (2023).
5. de Winter, B.C.M., Mathot, R.A., Sombogaard, F., Vulto, A.G. & van Gelder, T. Nonlinear relationship between mycophenolate mofetil dose and mycophenolic acid exposure: implications for therapeutic drug monitoring. *Clin. J. Am. Soc. Nephrol.* **6**, 656–663 (2011).
6. Knight, S.R. & Morris, P.J. Does the evidence support the use of mycophenolate mofetil therapeutic drug monitoring in clinical practice? A systematic review. *Transplantation* **85**, 1675–1685 (2008).
7. Kuypers, D.R.J. *et al*. Consensus report on therapeutic drug monitoring of mycophenolic acid in solid organ transplantation. *Clin. J. Am. Soc. Nephrol.* **5**, 341–358 (2010).
8. Sommerer, C. *et al*. Pharmacokinetic and pharmacodynamic analysis of enteric-coated mycophenolate sodium: limited sampling strategies and clinical outcome in renal transplant patients. *Br. J. Clin. Pharmacol.* **69**, 346–357 (2010).
9. Tett, S.E. *et al*. Mycophenolate, clinical pharmacokinetics, formulations, and methods for assessing drug exposure. *Transplant. Rev. (Orlando)* **25**, 47–57 (2011).
10. van Gelder, T. *et al*. Comparing mycophenolate mofetil regimens for de novo renal transplant recipients: the fixed-dose concentration-controlled trial. *Transplantation* **86**, 1043–1051 (2008).
11. Gaston, R.S. *et al*. Fixed- or controlled-dose mycophenolate mofetil with standard- or reduced-dose calcineurin inhibitors: the Opticept trial. *Am. J. Transplant.* **9**, 1607–1619 (2009).
12. Le Meur, Y. *et al*. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. *Am. J. Transplant.* **7**, 2496–2503 (2007).
13. Le Meur, Y. *et al*. Early steroid withdrawal and optimization of mycophenolic acid exposure in kidney transplant recipients receiving mycophenolate mofetil. *Transplantation* **92**, 1244–1251 (2011).
14. Le Guellec, C. *et al*. Population pharmacokinetics and Bayesian estimation of mycophenolic acid concentrations in stable renal transplant patients. *Clin. Pharmacokinet.* **43**, 253–266 (2004).
15. Prémaud, A. *et al*. Maximum a posteriori bayesian estimation of mycophenolic acid pharmacokinetics in renal transplant recipients at different postgrafting periods. *Ther. Drug Monit.* **27**, 354–361 (2005).
16. Musuamba, F.T. *et al*. Limited sampling models and Bayesian estimation for mycophenolic acid area under the curve prediction in stable renal transplant patients co-medicated with ciclosporin or sirolimus. *Clin. Pharmacokinet.* **48**, 745–758 (2009).
17. de Winter, B.C.M. *et al*. Bayesian estimation of mycophenolate mofetil in lung transplantation, using a population pharmacokinetic model developed in kidney and lung transplant recipients. *Clin. Pharmacokinet.* **51**, 29–39 (2012).
18. Saint-Marcoux, F., Vandierdonck, S., Prémaud, A., Debord, J., Rousseau, A. & Marquet, P. Large scale analysis of routine dose adjustments of mycophenolate mofetil based on global exposure in renal transplant patients. *Ther. Drug Monit.* **33**, 285–294 (2011).
19. Labriffe, M. *et al*. Mycophenolate mofetil dose adjustment in pediatric kidney transplant recipients. *Ther. Drug Monit.* **45**, 591–598 (2023).
20. Villeneuve, C. *et al*. Evolution and determinants of health-related quality-of-life in kidney transplant patients over the first 3 years after transplantation. *Transplantation* **100**, 640–647 (2016).
21. Villeneuve, C. *et al*. Adherence profiles in kidney transplant patients: causes and consequences. *Patient Educ. Couns.* **103**, 189–198 (2020).
22. Billat, P.A. *et al*. Multidrug resistance-associated protein 4 (MRP4) controls ganciclovir intracellular accumulation and contributes to ganciclovir-induced neutropenia in renal transplant patients. *Pharmacol. Res.* **111**, 501–508 (2016).
23. Stamenic, D. *et al*. A prognostic tool for individualized prediction of graft failure risk within ten years after kidney transplantation. *J. Transp. Secur.* **2019**, 7245142 (2019).
24. Rosenbaum, P.R. & Rubin, D.B. The central role of the propensity score in observational studies for causal effects. *Biometrika* **70**, 41–55 (1983).
25. van Gelder, T. *et al*. Renal transplant patients at high risk of acute rejection benefit from adequate exposure to mycophenolic acid. *Transplantation* **89**, 595–599 (2010).
26. Brooks, J.M. & Ohsfeldt, R.L. Squeezing the balloon: propensity scores and unmeasured covariate balance. *Health Serv. Res.* **48**, 1487–1507 (2013).
27. Okoli, G.N., Sanders, R.D. & Myles, P. Demystifying propensity scores. *Br. J. Anaesth.* **112**, 13–15 (2014).
28. Cho, H., Yu, H., Shin, E., Kim, Y.H., Park, S.K. & Jo, M.W. Risk factors for graft failure and death following geriatric renal transplantation. *PLoS One* **11**, e0153410 (2016).
29. Ojo, A.O., Wolfe, R.A., Held, P.J., Port, F.K. & Schmouder, R.L. Delayed graft function: risk factors and implications for renal allograft survival. *Transplantation* **63**, 968–974 (1997).
30. Betjes, M.G.H., Sablik, K.S., Otten, H.G., Roelen, D.L., Claas, F.H. & de Weerd, A. Pretransplant donor-specific anti-HLA antibodies and the risk for rejection-related graft failure of kidney allografts. *J. Transplant.* **2020**, 5694670 (2020).
31. US Food and Drug Administration. Guidance for industry and Food and Drug Administration staff: use of real-world evidence to support regulatory decision-making for medical devices <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/use-real-world-evidence-support-regulatory-decision-making-medical-devices> (2017) Accessed December 9, 2023.